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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,942	BASI ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,13-41,62,169,171,173,175,177,179,181,183,185,187,189,191,193,195,197-206* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7,13-41,62,169,171,173,175,177,179,181,183,185,187,189,191,193,195,197-206* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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RESPONSE TO AMENDMENT

Status of Application, Amendments, and/or Claims

1. Applicant's amendment filed 19 May 2005 is acknowledged. Claims 6, 7, 13-41, 62, 169, 171, 173, 175, 177, 181, 183, 185, 187, 189, 191, 193, 195, and 197-206 are pending and under examination in this office action. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

2. The Examiner of U.S. Patent Application No. 10/010,942 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Ballard, Technology Center 1600, Art Unit 1649.

3. The ATCC deposit receipt, response and amendment filed May 19, 2005 have been received and entered.

Withdrawn Objections and/or Rejections

4. The objection to the specification as set forth at p. 3 ¶9 in the previous office action (January 19, 2005) is hereby *withdrawn* in view of Applicant's response dated May 19, 2005.

5. The provisional statutory double patenting rejection as set forth at p. 4 ¶10 in the previous office action (January 19, 2005) regarding copending Application No. 10/232,030 are *withdrawn* in view of Applicant's amendments to the claims (May 19, 2005).

6. The provisional statutory double patenting rejection as set forth at p. 4 ¶11 in the previous office action (January 19, 2005) of claims 32, 38, and 62 of the instant application regarding copending Application No. 10/388,389 are *withdrawn* in view of Applicant's amendments to the claims (May 19, 2005).

7. The rejection of claims 1-41, 62, and 165-206 under U.S.C. §112 ¶1 as set forth at pp.4-6 ¶13-16 in the previous office action (January 19, 2005) is *withdrawn* in view of Applicant's amendments (May 19, 2005).

Information Disclosure Statement

8. The information disclosure statement (IDS) filed on May 24, 2005 has been considered. However, references # 632, 653, and 637 will not be printed because they do not have publication dates and #648 will not be printed because it does not have a title.

Double Patenting

Statutory Double Patenting

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Applicant's request to withdraw the provisional statutory double patenting rejections in the Response filed May 19, 2005 has been taken into consideration and is not found persuasive. The rejection under 35 U.S.C. for provisional statutory double patenting of claims 6-7, 13-31, 33-37, and 39-41 of the instant application over

Application No. 10/388,389 is proper and will remain in effect until Applicant amends the claims of these Applications allowable subject matter is identified, until they are no longer in conflict or in the event of abandonment.

Obvious-Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 32, 38, 62, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197-206 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 32 (including claims 13, 14, 30, and 31), 62, and 15-29 of copending Application No. 10/388,389. Although the conflicting claims are not identical, they are not patentably distinct from each other because the humanized immunoglobulin, antigen binding fragments, light chains, heavy chains, and pharmaceutical compositions comprising the immunoglobulin of Application No. 10/388,389 encompass the humanized immunoglobulin, antigen

binding fragments, immunoglobulin light and heavy chains, and pharmaceutical compositions instantly claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 6, 7, 13-41, 62, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197-206 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 51, 227-230, 232-248, 251, and 284 of copending Application No. 10/232,030. Although the conflicting claims are not identical, they are not patentably distinct from each other because the humanized antibodies, antigen-binding fragments, and pharmaceutical compositions comprising the humanized antibody or antigen-binding fragments of Application No. 10/232,030 encompass the humanized immunoglobulin, antigen binding fragments, immunoglobulin light and heavy chains, and pharmaceutical compositions instantly claimed. The claims of each application are overlapping in scope; the fragments are merely described differently. The '030 application defines antigen-binding fragments as polypeptide fragments of an immunoglobulin or antibody which binds antigen or competes with the intact antibody from which they were derived (p. 11, lines 13-15), which would meet the limitations of the claims presented in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 6, 7, 13, 14, 32, 33-41, 62, 195, and 197-206 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 9, 23, and 31-40 of copending Application No. 10/703,713. Although the conflicting claims are not identical, they are not patentably distinct from each other because the humanized antibodies, antigen-binding fragments, and pharmaceutical compositions comprising the humanized antibody or antigen-binding fragments of Application No. 10/232,030 encompass the humanized immunoglobulin, antigen binding fragments, immunoglobulin light and heavy chains, and pharmaceutical compositions instantly claimed. The claims of each application are overlapping in scope; the fragments are merely described differently. The '030 application defines antigen-binding fragments as polypeptide fragments of an immunoglobulin or antibody which binds antigen or competes with the intact antibody from which they were derived (p. 12, lines 26-29), which would meet the limitations of the claims presented in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention

was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 6, 7, 13, 14-41, 62, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, and 197-206 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson-Wood et al., *Proc. Natl. Acad. Sci. USA*, February 1997, Vol. 94, pp. 1550-1555 in view of U.S. Patent No. 5,530,101 to Queen et al. and in further view of Frenkel et al., *J. Neuroimmunology*, July 2000, Vol. 106, pp. 23-31.

The claims recite a humanized immunoglobulin light chain comprising (i) variable region complementarity determining regions (CDRs) from the mouse monoclonal antibody 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and (ii) a variable framework region from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence. The claims also recite a humanized immunoglobulin heavy chain comprising

(i) variable region CDRs from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and (ii) variable framework region from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence. The claims further recite designations of the acceptor light and heavy chain subtypes and sequences, amino acid substitutions, specific binding affinities, binding to both soluble, aggregated and disaggregated Aβ, mediation of phagocytosis of Aβ, ability to cross the blood-brain barrier, reduction of both beta amyloid peptide burden and neuritic dystrophy in a subject, and pharmaceutical compositions comprising the immunoglobulin or an antigen binding fragment and a pharmaceutical carrier.

The claims are directed to humanized immunoglobulin light and heavy chains of 3D6 antibody, antigen binding fragments, and pharmaceutical compositions comprising said immunoglobulins and antigen binding fragments. The specification teaches antigen binding fragments as referring to a polypeptide fragment of an immunoglobulin or antibody [that] binds antigen or competes with intact antibody (*i.e.*, with the intact antibody from which they were derived) for antigen binding (*i.e.*, specific binding). The specification further teaches that binding fragments include Fab, Fab', $F(ab')_2$, Fabc, Fv, single chains, and single-chain antibodies. The specification further teaches that humanized immunoglobulin chain (*i.e.*, a humanized immunoglobulin light chain or humanized immunoglobulin heavy chain) refers to an immunoglobulin or antibody chain (i.e., a light or heavy chain, respectively) having a variable region that includes a

variable framework region substantially from a human immunoglobulin or antibody and CDRs substantially from a non-human immunoglobulin or antibody, and further includes constant regions (e.g., at least one constant region or portion thereof, in the case of a light chain, and preferably three constant regions in the case of a heavy chain).

Johnson-Wood et al. teach a monoclonal antibody 3D6, which is specific for Aβ1-5 used to determine Aβ and APP immunoreactivities in the PDAPP mouse brain, a transgenic mouse model of Alzheimer's disease. The reference does not teach an immunoglobulin light chain variable region sequence of SEQ ID NO:2, an immunoglobulin heavy chain variable region sequence of SEQ ID NO:4, variable region framework residues L1, L2, L36, L46, H49, H93, and H94 (Kabat numbering convention), or the substitutions or acceptor chain designations as recited in claims 6, 7, 13, 14-32, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, and 197. Although the reference does not teach the sequences for the CDRs from the 3D6 monoclonal antibody, these are intrinsic properties of the 3D6 antibody. Also, it is an inherent property of the 3D6 immunoglobulin light and heavy chains to bind to the same antigen as the original antibody. Therefore, the light and heavy chain CDRs instantly claimed are unpatentable over the prior art as the sequences are intrinsic properties of the antibody. Further, the claim limitations of heavy chain isotype γ1, binding to soluble, aggregated, and disaggregated Aβ, mediating phagocytosis of Aβ, crossing the blood-brain barrier, and reducing both the Aβ burden and neuritic dystrophy in a subject (as in claims 36-41) would also all be intrinsic properties of immunoglobulin chains derived from the 3D6 antibody and therefore are also all unpatentable over the prior art.

Johnson-Wood et al. also does not teach humanized antibodies; however, the '101 patent discloses methods for preparing humanized immunoglobulin chains having generally one or more complementarity determining regions (CDRs) from a donor immunoglobulin and a framework region from a human immunoglobulin. The CDRs for producing the immunoglobulins disclosed are derived from monoclonal antibodies capable of binding to the predetermined antigen (Col. 16, lines 63-67). The patent discloses that humanized antibodies are important because they bind to the same antigen as the original antibodies, but are less immunogenic when injected into humans (see Background of the Invention, Col. 1-2).

The '101 patent discloses methods for producing and compositions of humanized antibodies having one or more CDRs from a donor immunoglobulin, and a human acceptor immunoglobulin having the highest homology to the donor immunoglobulin sequences of any sequence in the collection (Col. 2). The humanized immunoglobulins will have a human framework and have one or more CDRs plus a limited number of other amino acids from a donor immunoglobulin specifically reactive with an antigen (Col. 10, lines 61-65). The CDRs can be derived from monoclonal antibodies capable of binding a predetermined antigen (Col. 16-17). The donor immunoglobulin may be either a heavy or a light chain, and the human collection will contain the same kind of chain. Humanized light and heavy chains can then be used to form a complete humanized immunoglobulin or antibody (Col. 2, lines 53-57).

The '101 patent discloses that the amino acids in the acceptor immunoglobulin chain may be replaced with amino acids from the donor immunoglobulin chain if: (1) the

donor immunoglobulin amino acid is in a CDR, (2) the amino acid in the human framework region of the acceptor immunoglobulin is rare for that position and the corresponding amino acid in the donor immunoglobulin is common for that position in human immunoglobulin sequences (as recited in claims 21, 24, 181, and 187 of the present invention); (3) the amino acid is immediately adjacent to one of the CDRs; or (4) the amino acid is capable of interacting with the antigen or with the CDRs of the donor or humanized immunoglobulin (column 2, line 60 - column 3, line 25). Additionally, the '101 patent discloses that "rare" amino acids are interpreted to include amino acids that occur in usually less than about 10% of the human sequences and "common" amino acids are interpreted to include amino acids that occur in more than about 25% but generally more than 50% of the human sequences (Col. 14, lines 1-13) as in claims 28, 29, 195, and 197 of the present invention.

The '101 patent discloses humanized antibodies, which are intact and single chain (Col. 17, line 41) as in claims 6, 7, 13, 14-41, 62, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, and 197 of the instant application. The '101 patent discloses the immunoglobulins, including binding fragments and other derivatives thereof, of the present invention that may be produced readily by a variety of recombinant DNA techniques (Col. 22, line 22).

In designing humanized light and heavy chains, the '101 patent discloses that the more homologous a human antibody is to the original murine antibody, the less likely will combining the murine CDRs with the human framework be to introduce distortions into the CDRs that could reduce affinity (Col. 54, lines 29-33, and further detailed in

Col.13, lines 6-56). The patent also discloses that in selection of an acceptor immunoglobulin chain, a framework immunoglobulin may also use a consensus framework from many human antibodies (Col. 13, lines 6-9). As the Applicant indicates, the light chain subtype kappa II acceptor (Kabat ID 019230), heavy chain subtype III acceptor (Kabat ID 045919), and the human germline V regions sequences (as recited in claims 15-20, 22, 23, 25-27, 169, 171, 173, 175, 177, 179, 183, 189, 191, and 193) exhibit a high degree of homology with the subject sequence. The '101 further discloses that higher affinity may be achieved by selecting a small number of amino acids in the framework of the humanized immunoglobulin chain to be the same as the amino acids at those positions in the donor rather than in the acceptor, as in claims 13, 14, and 32 of the instant application.

The '101 patent discloses humanized immunoglobulins having binding affinities of at least about 10^8 M^{-1}, and preferably 10^9 M^{-1} to 10^{10} M^{-1} or stronger (Col. 10, lines 55-61) as in claims 33-35 of the present invention.

Finally, the '101 patent discloses pharmaceutical compositions comprising humanized antibodies and a pharmaceuticially acceptable carrier as in claims 62 and 198-206 of the instant application (Col. 23, lines 23-56).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Johnson-Wood et al. demonstrating the ability of the 3D6 monoclonal antibody to selectively bind to Aβ in the brains of mice to produce humanized antibodies as taught in U.S. Patent 5,530,101 that bind beta amyloid in humans. The person of ordinary skill in the art would have been motivated to

modify the teachings of Johnson-Wood et al. to make a humanized immunoglobulins and a pharmaceutical composition as claimed because Johnson-Wood et al. teaches using the 3D6 antibodies to measure Aβ levels in PDAPP transgenic mice, which overexpress human APP and develop much of the pathology associated with Alzheimer's disease. The person of ordinary skill in the art would have been further motivated by the teachings of Frenkel et al. to produce the antibody fragments of light and heavy chain immunoglobulins because Frenkel et al. teach that difficulties associated with delivery of Aβ-specific anti-aggregating monoclonal antibodies to the brain (due to the presence of the blood-brain barrier) can be minimized through the use of single-chain antibodies, which can penetrate the BBB. The artisan would have expected success because the humanized immunoglobulin light and heavy chains produced would bind to the same antigen as the original antibody, human 3D6, but are less immunogenic in humans according to the '101 patent (Abstract).

Conclusion

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kimberly A. Ballard, Ph.D.
Art Unit 1649
September 28, 2005

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER